

news and views

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Cancer: Checkpoint for invasion

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Both benign and malignant tumours grow in an uncontrolled way. But it is only cells of malignant tumours that invade surrounding tissues and travel to distant organs (metastasize). Conventional wisdom used to hold that invasion and metastasis are late events — often 'too late' — in the clinical course of a patient's cancer. However, we now know that invasion can be both early and clinically 'silent'. An understanding of the molecular basis for this aggressiveness could lead to therapies that block the transition of a tumour from benign to malignant, and keep local disease in check. Taguchi and colleagues¹, writing on page 354 of this issue, have now identified proteins called RAGE and amphoterin as a receptor–ligand pair in a molecular checkpoint that regulates not only the invasiveness but also the growth and movement of tumour cells — the trio of characteristics required for malignancy.

The threat of tumour invasiveness is exemplified by the fact that brain cancer does not need to metastasize to kill a patient. The growth of a brain tumour mass in the confined area of the skull causes compression damage; in addition, local invasion by brain tumour cells can destroy surrounding, normal brain tissue. In many cases, brain tumour cells can move away from the primary tumour to reach other sites within the brain. Such insidious invasive behaviour may represent the inappropriate use of a programme responsible for the outgrowth of neuronal protrusions called neurites during normal neuronal development. Indeed, cancer invasion in general may be a deregulated form of a physiological invasion process required for neuronal wiring in the embryo, tissue remodelling, the formation of blood vessels, and healing².

Amphoterin is a key protein in normal neurite outgrowth. It is a heparin-binding protein that is abundant in extracellular regions of the developing brain and other organs. Antibodies that recognize amphoterin block neurite outgrowth under experimental conditions; so, interactions of amphoterin with neuronal surfaces appear to be required for the extension of neuronal processes. Amphoterin's receptor on the cell surface is protein called RAGE (for 'receptor for advanced glycation end products')³. RAGE is a receptor for many different ligands, and is a member of the immunoglobulin superfamily of cell-surface molecules. It gains its name, and was first identified, because it recognizes potentially damaged, glycated proteins (that is, those with carbohydrate polymers attached to them) that accumulate during diabetes. Amphoterin and RAGE localize together at the leading edge of advancing neurites during embryonic development³. Taguchi *et al.*¹ recognized the implications of this result for pathological processes such as cancer invasion.

The complete set of characteristics of a malignant tumour is induced by a variety of cellular programmes and pathways, many of which are not yet fully defined. Faced with this complexity, the best way to link a molecule causally to malignancy is to start with a cell that is already malignant, and to attempt to block the molecule or pathway of interest. This was the tack taken by Taguchi *et al.*¹, who used several approaches block the RAGE–amphoterin axis in C6 glioma brain tumour cells. Inhibitory strategies included administering the soluble form of the ligand-binding domain of RAGE, of anti-RAGE antibodies, or of anti-amphoterin antibodies, or introducing defective forms of RAGE into C6 glioma cells. *In vitro* and in animal models of cancer, all of these treatments significantly inhibited the growth, motility and local

invasion of tumour cells, as well as metastasis of the cells to the lungs. The treatments even inhibited the spontaneous growth of papillomas (benign skin cancers) in mice overexpressing the v-Ha-ras oncogene. How might the RAGE-amphotericin pathway have these effects?

Let's take a look first at invasion. Regulation of the molecular events necessary for invasion — whether physiological or malignant — involves spatial and temporal coordination, as well as cyclic on-off processes, at the level of individual cells (Fig. 1). Motility, coupled with regulated, intermittent adhesion to the extracellular matrix and degradation of matrix molecules, allows an invading cell to move through the three-dimensional matrix. At the leading edge of the motile cell, receptor-ligand and proteolysis-antiproteolysis complexes coordinate sensing, protrusion, burrowing and traction of the cell^{4, 5}.

Figure 1 Spatial and temporal regulation of cellular invasion of the extracellular matrix. Full legend

High resolution image and legend (34k)



It was already known that amphotericin at the cell surface can act as a nucleating site for generation of the protein-degrading complex plasmin⁶. This complex can activate matrix metalloproteinases (MMPs), which are enzymes that degrade extracellular matrix molecules⁵. Taguchi *et al.*¹ now report that blocking RAGE results in decreased activity of MMP-2 and MMP-9 — molecules previously associated with invasion of both cancer cells and neurites. Localized proteolysis of matrix molecules may loosen up, or open up, the dense meshwork of matrix molecules being invaded. Proteolysis at the migration front may also liberate previously bound growth factors or motility-stimulating molecules.

The RAGE-amphotericin complex also suppresses tumour growth, but how does it coordinate these three inhibitory effects — on growth, on motility and on invasion? Proteins called cytokines, as well as proteins found in the extracellular matrix, trigger signalling cascades that regulate both cell migration and proliferation. Bifurcation of this signalling pathway occurs at the level of mitogen-activated protein kinase (MAPK) signalling modules. Three coexisting modules — p38^{MAPK}, JNK and p42/p44^{MAPK} — exchange signals between the cell surface, the cytoskeleton and the nucleus.

When a ligand stimulates the cell through that ligand's receptor, some or all of these MAPK modules can be activated, directly or indirectly, as can the small GTP-hydrolysing proteins (GTPases) Ras, Cdc42, Rac and Rho^{7, 8}. Activated MAPK modules propagate signals downstream into the nucleus to activate genes encoding growth inducers, MMPs and adhesion receptors. In parallel, these modules elicit further events that modify the myosin and actin filaments of the cytoskeleton. So all three MAPK modules can act as relay stations for the regulation of growth, motility and invasion. Taguchi *et al.*¹ show that RAGE-amphotericin acts simultaneously through all three MAPK modules, explaining how blocking RAGE will experimentally suppress all components of the malignant phenotype.

'Signal-transduction therapy' is a treatment strategy in which key, hyperactive cellular signalling pathways that cause disease are targeted. The trick is to find a rheostat in the cell's circuitry that is not bypassed by collateral or compensatory paths. The RAGE-amphotericin pathway may well fulfil these criteria.

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